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A case of oculo-cerebral B-cell lymphoma in a cat

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Abstract

Purpose: To describe a case of a cat with primary B-cell lymphoma affecting the eye and brain and which shared features similar to oculo-cerebral lymphoma in humans.

Methods: A 13-year-old castrated male Persian cat presented with clinical signs of anterior uveitis and increased intraocular pressure (IOP) in the left eye (OS). A complete diagnostic work-up was declined, and left-eye enucleation was performed. The globe was submitted for histopathology. One week after surgery, the cat became inappetent, hypothermic, and aggressive. Euthanasia was requested by the owner, and a necropsy was permitted.

Results: Histopathology of the enucleated globe revealed an extensive neoplastic infiltration consistent with large-cell lymphoma, affecting the anterior uvea, neuroretina and optic nerve. At necropsy, all organs were unremarkable except for the brain, where there was a neoplastic cell population consistent with that described in the left eye, infiltrated and expanded meninges, and perivascular spaces. Immunohistochemically, the neoplastic cells were positive for B-cell marker (CD20) and negative for T-cell marker (CD3). Histology and immunophenotyping suggested a diagnosis of primary central nervous system and ocular large B-cell lymphoma.

Discussion The lymphoma in this cat resembled oculo-cerebral lymphoma in humans, sharing similar clinical features and histopathological findings, including the perivascular pattern of neoplastic cell infiltration. To the best of the authors' knowledge, this is the first description of a primary oculo-cerebral B-cell lymphoma in a cat.

Key Words: central nervous system, eye, feline, histology, immunophenotyping, lymphoma

INTRODUCTION

Ocular lymphoma is the second most common intraocular neoplasm in cats. It is generally considered to be metastatic, although the ocular disease is frequently the presenting complaint and may precede signs of systemic involvement.¹⁻⁴ The most commonly involved ocular tissue is the anterior uvea (iris and ciliary body), although the choroid, retina, optic nerve, and cornea may also be affected.¹ Both primary and secondary intraocular lymphomas have been reported in humans.⁵⁻⁷

For many years, nonmetastatic ocular lymphomas were subsumed under the generic nomenclature of primary intraocular lymphoma (PIOL).⁷ As intraocular lymphomas represent, in fact, distinct entities with a different clinical course and prognosis, the use of this nomenclature has been recently discouraged. Instead, three main groups of lymphomas occurring in intraocular structures are now distinguished: primary retinal lymphoma, primary uveal (choroidal, ciliary body, and iridal) lymphoma, and secondary intraocular (uveal) lymphoma.^{5,8} Retinal lymphoma is the most common of these entities in humans. It generally occurs in elderly patients and usually presents in isolation, although subclinically central nervous system (CNS) involvement develops in 80% of cases before or subsequent to the ocular manifestations. The combined manifestation of cerebral and ocular involvement is also referred to as oculo-cerebral lymphoma or ocular central nervous system lymphoma (OCNSL).⁸ To the best of the authors' knowledge, neither a primary intraocular lymphoma nor the association of intraocular and intracranial lymphomas has been reported so far in cats. This report describes a case of B-cell lymphoma confined to the eye and the CNS in a cat, without concurrent evidence of systemic involvement. Its similarities to OCNSL in humans are discussed.

CASE REPORT

Signalment, history, and clinical findings

A 13-year-old castrated male indoor Persian cat presented with a 4-week history of a change in iris color and anisocoria characterized by miosis OS. The cat was regularly vaccinated and otherwise in good health. No history of trauma or previous medication or exposure to chemicals or toxins was reported. Empirical therapy with topical tobramycin (Tobral, Alcon, Italy), dexamethasone (Tobradex, Alcon), and propentofylline (Karvisan, Intervet, Italy) was initiated without success prior to referral. Vital signs (heart rate, respiratory rate, and temperature) and the physical exam were normal. Ophthalmologic examination of the left eye revealed absence of the menace response, dazzle reflex, and direct and consensual pupillary light reflex (PLRs). The palpebral reflex was normal. Based on these findings, the left eye was considered functionally blind. The Schirmer tear test was normal. As measured by applanation tonometry (Tonopen XL; Mentor, Norwell, MA), the intraocular pressure (IOP) was 42 mm Hg (normal IOP in the cat, 19.7 ± 5.6 mm Hg⁹). Moderate episcleral congestion, moderate conjunctival hyperemia, and mild corneal edema were present. Fluorescein uptake was positive surrounding the corneal sequestrum because it was associated with loose epithelial margins. Examination of the anterior segment by slit-lamp biomicroscopy (Kowa SL 14; Kowa, Tokyo, Japan) revealed diffuse iris swelling with fibrin clots and hypopyon. Posterior synechiae from the 7–12 o'clock position were also noted. Lens and ocular fundus examination were precluded by the presence of corneal edema, anterior chamber turbidity, and posterior synechia. Ophthalmologic examination of the right eye was normal. A diagnosis of left anterior uveitis with secondary glaucoma and ulcerative exposure keratitis was made. The main differential diagnosis included neoplastic (primary or metastatic intraocular neoplasia), infectious, or idiopathic/immune-mediated diseases. Cell blood count and serum biochemistry profile results were within normal limits. The owner declined further diagnostic work-up with appropriate serologies, urinalysis, thoracic radiography, ocular and abdominal ultrasound, and aqueous cytology.

Surgical procedure and follow-up

Because of the blindness, the severity, and extent of the lesions, the owner elected left-eye enucleation. Enucleation was performed 2 days following referral, and surgery was routine. The globe was fixed intact in 10% neutral buffered formalin and submitted for histology. Postoperative medication included oral systemic cefalexin 20 mg/kg q12 h for 7 days (Rilexine 75 mg; Virbac Italia, Italy). One week after surgery, the cat became inappetent, hypothermic, and aggressive. The owner declined additional investigation including neurologic consultation and elected euthanasia instead. Complete necropsy was performed.

Histopathology and immunohistochemistry

The left eye globe, after formalin fixation for about 48 h, was sectioned in a vertical plane section passing through the optic nerve. Both calottes were paraffin-embedded and routinely processed for histology. Five-micrometer sections were obtained from the paraffin blocks and were stained using hematoxylin and eosin. Histologically, the eye architecture was severely effaced by neoplastic infiltration involving the anterior uvea and sensory retina. In the anterior uvea, the neoplastic cells were arranged in dense sheets, expanding the iris and ciliary body stroma, and extending multifocally to the filtration angle. Within the sensory retina, the neoplastic cells were arranged perivascularly, forming large cuffs around the arteriolar vessels (Fig. 1). The optic nerve and meninges were also diffusely infiltrated. The neoplastic cells were round, about 15–17 μ m in diameter, with distinct cell borders, a moderate amount of eosinophilic cytoplasm and large, vesicular indented nuclei with a single prominent nucleolus. Marked anisocytosis and anisokaryosis, with occasional binucleated cells, and 1–2 mitotic figures per high-power field (400 \times) were detectable. Large areas of coagulative necrosis and intense neutrophilic infiltration were also present within the iridal stroma. Hypopyon, neutrophilic hyalitis, cystoid degeneration of the pars plana retinae, and wide central corneal ulceration with neutrophilic infiltration and neovascularization of the underlying stroma were also detectable. A histological diagnosis of intraocular large B-cell lymphoma was posed. At complete necropsy, all organs including the right eye were grossly and histologically unremarkable, except for the brain. Histologically, the neoplastic cells were morphologically consistent with those described in the left eye. They infiltrated and expanded diffusely into the meninges around the optic nerve and the brain; in the frontal lobe, they extended caudally into the subthalamus and brainstem; as observed in the retina, the neoplastic cells showed a prominent perivascular arrangement (Fig. 2), expanding multifocally into the perivascular spaces (Virchow's spaces). For immunophenotyping of the lymphoma, immunohistochemical analysis on serial sections of the left eye and the CNS was performed using the standard avidin–biotin–peroxidase complex (ABC) method. Antigen was retrieved by incubating the slides in citrate buffer (pH 6.0) in a conventional pressure steamer for 10 min. The slides were then incubated overnight (4 LC) with rat monoclonal anti-CD3 antibody (Prof. Peter Moore, Davis, CA; dilution 1:10) and rabbit polyclonal anti-CD20 antibody (Thermo Scientific, Fremont, CA; dilution 1:400). AEC Substrate Kit (Vector Laboratories, Milano, Italy) served as the chromogen. The sections were counterstained with Mayer's hematoxylin. All staining was performed in parallel with appropriate positive and negative controls. Immunohistochemically, the neoplastic cells infiltrating the left eye and the CNS stained consistently and intensely positive with CD20 (Fig. 3) and were always negative for CD3. Based on histological findings and neoplastic cell immunophenotyping, a diagnosis of primary oculo-cerebral B-cell lymphoma was posed.

DISCUSSION

The presenting signs of miosis, discolored iris, inappetence, hypothermia, and behavior changes (aggression) exhibited by this cat were attributed to the uveitis and brain involvement, respectively.

In humans, primary intraocular lymphoma usually manifests itself as a nonspecific uveitis, initially responsive but later resistant to corticosteroid therapy, most frequently with unilateral or prominent monolateral involvement.^{10,11} When the CNS is also involved, the reported frequency of ocular, neuropsychiatric, and gastro- enteric symptoms, secondary to the raised intracranial pressure, is 4%, 43%, and 33%, respectively.¹² Unfortunately, the authors were unable to examine the neurologic clinical signs in this cat as the owner did not consent further investigation. To the authors' knowledge, this is the first description of a B-cell lymphoma confined to the eye and the brain in the feline species. While primary intracranial B-cell lymphomas have been documented in the feline species, neither concomitant CNS and ocular tissue involvement nor primary intra- ocular lymphoma has been reported so far in cats.^{13,14} In a previously reported case of primary intracranial lymphoma, subretinal lesions were clinically observed in the left eye, but because histological examination of eye tissue was not per- formed, a lymphoma could not definitively ruled out in that tissue.¹⁴ Most intraocular lymphomas reported in the feline species were associated with systemic disease, and ocular lymphoma in cats is generally considered a metastatic localization.^{1,15} In humans, primary intraocular lymphoma is a well- known entity that is further divided into primary uveal and primary retinal lymphoma, the latter being the most commonly reported form.^{5,7,16} Retinal lymphoma is described as a non-Hodgkin, high-grade, diffuse large B-cell lymphoma (DLBCL) affecting the sensory retina, retinal pigment epithelium, vitreous, optic nerve and, more rarely, extending to the anterior uveal tract. It can occur independently of or, more commonly, in association with CNS lymphoma, in which case it is referred to as OCNSL.^{6,11} Although ocular signs are often the presenting complaint, tumors apparently arising in the retina may actually have developed from an occult primary CNS neoplasm.¹⁷ As the retina and the optic nerve are both part of the CNS, it has also been argued that lymphoma arising in the sensory retina, optic nerve, and retinal pigment epithelium should be considered as a primary CNS lymphoma with secondary intraocular extension. Accordingly, the distribution of primary intraocular lymphoma subtypes is similar to that of lymphoma subtypes in the CNS.¹¹ The systemic dissemination of retinal lymphoma is extremely rare; nevertheless, the prognosis is poor, probably due to CNS involvement. In this cat, although the ocular signs developed first, an occult primary CNS lymphoma could not be fully excluded. However, although a complete ante-mortem work-up was not conducted, concurrent systemic neoplastic involvement and the possibility that the eye and the CNS were metastatic locations of a systemic disease were subsequently ruled out by the postmortem examination of all tissues and organs. In human medicine, a characteristic histological feature of cerebral and retinal lymphoma is the perivascular pattern of infiltration of neoplastic cells, forming dense cuffs around cerebral blood vessels and mimicking, ophthalmoscopically, retinal vasculitis.^{6,7,10} A similar growth pattern of neoplastic cells has also been reported in primary cerebral lymphoma in humans and feline species.¹⁸⁻²⁰ In this cat, the neoplastic cells were typically clustered perivascularly in the sensory retina and brain meninges. A similar pattern of distribution could not be identified within the iridal stroma where the extensive necrosis, possibly due to vascular lesions, obliterated any recognizable pattern. In humans, most retinal and CNS lymphomas are large B-cell lymphomas, while T-cell lymphomas account for only a minority of cases.¹⁰ In the feline species, primary CNS lymphomas have been reported as T- or B-cell lymphomas. But because immunophenotyping of feline ocular lympho- mas has rarely been performed, no definite conclusions can be drawn concerning the incidence of the T- and B-cell phenotype, respectively, or its prognostic significance.^{13,14,19,20} In general terms, because ocular lymphomas are usually secondary tumors, the immunophenotype depends on the subtype of primary lymphoma. According to one study, feline B-cell ocular lymphoma is diagnosed about twice as frequently as T-cell lymphoma.²¹ The authors suggested that all intraocular lymphomas were likely metastatic, although the hypothesis of a neoplastic transformation of lymphocytes infiltrating the uveal tissues secondary to uveitis could not be completely discarded. In this case, based on the immunohistochemical analysis, a large B-cell ocular and cerebral lymphoma was diagnosed, consistent with most human OCNSL. As the CNS and the eye are normally devoid of lymphoid tissue, the understanding of the molecular

mechanisms underlying the pathogenesis of primary intracranial and intraocular lymphoma is quite limited. In human medicine, because of its association with the Epstein–Barr virus (EBV) in immunodeficient individuals, an immunologic response to EBV infection has been conjectured as the mechanism for its development.²² Similarly, some cases of primary intraocular lymphoma have been reported to be associated with microorganisms, including EBV, human herpes-virus-8, and *Toxoplasma gondii*.^{22,23} However, in the last years, the incidence of retinal lymphomas has increased dramatically, even in immunocompetent patients, suggesting that so far unknown, multifactorial events, including infections and immunosuppression, could play a role in lymphomagenesis.²⁴ In the cat, nonsuppurative meningoencephalomyelitis with perivascular mononuclear cuffing, neuronal damage, and inflammatory nodules has been associated with viral infections (i.e. feline immunodeficiency virus [FIV], feline leukemia virus [FeLV], feline infectious peritonitis [FIP]),^{25,26} and a percentage of cats with intracranial lymphoma test positive for FeLV.²⁷ However, no relationship has hitherto been drawn between FIV/FeLV infection and cerebral or ocular lymphoma. The FIV, FeLV, and FIP status of the cat described here was unknown. Although the clinical signs and laboratory findings were not suggestive of viral infection, definite evidence for its absence could not be clearly demonstrated and so remains speculative at best. In conclusion, this case describes, for the first time, a primary B-cell lymphoma confined to the brain and ocular tissue in a cat, without concurrent systemic involvement.

Figure 1. Histological section of the retina: neoplastic cells are clustered around arteriolar vessel forming a large, dense cuff (Hematoxylin and Eosin, 200x).

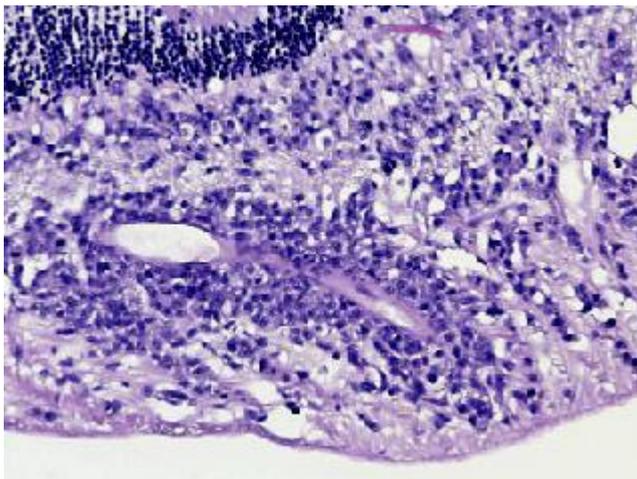


Figure 2. Histological section of the brain: a dense cuff of neoplastic cells expand a perivascular space (Hematoxylin and Eosin, 200x).

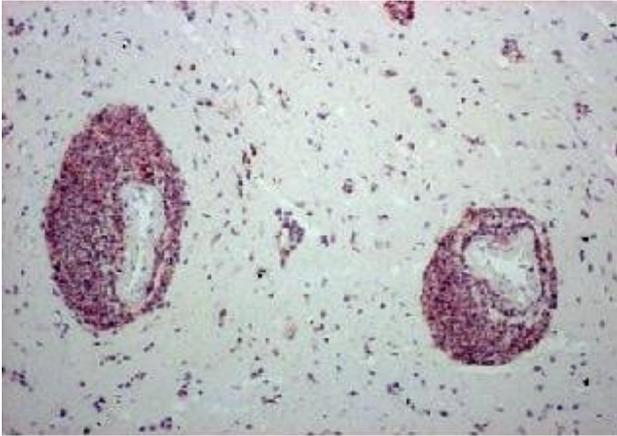
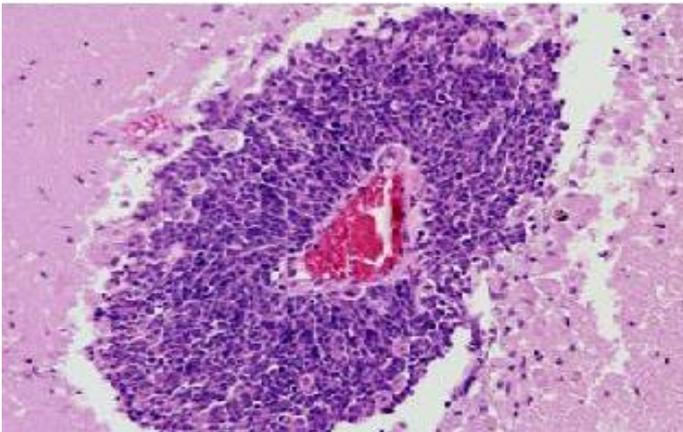


Figure 3. Histological section of the brain: neoplastic cells forming perivascular cuffs are diffusely immunohistochemically positive (red staining) for CD20 antibody, consistently with B-cell lymphoma (ABC standard method, AEC chromogen).



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